

Do measurements of inflammatory mediators in blood predict recurrence in patients with bisphosphonate-related osteonecrosis of the jaws?

Thomas Mücke^{a,*}, Maximilian Jung^a, David A. Mitchell^b, Klaus-Dietrich Wolff^a, Stefan Wagenpfeil^a, Philipp Stockmann^a, Marco Rainer Kesting^a, Herbert Deppe^a

^a Department of Oral and Maxillofacial Surgery, Technische Universität München, Klinikum Rechts der Isar, Munich, Germany

^b Bradford Teaching Hospitals NHS Foundation Trust, Maxillofacial Unit, St. Lukes Hospital, Bradford, UK

Accepted 3 January 2016

Available online 23 January 2016

Abstract

Bisphosphonate-related osteonecrosis of the jaws (BRONJ) is well-recognised, difficult to manage, and often recurs. The aim of this study was to examine the value of preoperative measurements of inflammatory mediators in blood in 212 patients with BRONJ who were studied prospectively. Multiple logistic regression analysis was used to assess the importance of the amounts of substances in the blood that are independently associated with the dependent variable “recurrence of BRONJ”. The only factor that significantly influenced the development of recurrent BRONJ was reduction in the white cell count ($p < 0.0001$; hazard ratio 5.324; 95% CI 2.373 to 11.945). Neither white cell counts nor C-reactive protein concentrations within or above the reference ranges were significantly associated with recurrent BRONJ. Patients whose white cell counts were lower than the reference range were at increased risk of recurrent BRONJ. This may be a marker of reduced immunocompetence, and additional prophylactic measures or treatment should be considered for these patients.

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Keywords: Bisphosphonates; Jaws; Osteonecrosis; Treatment outcome; Recurrence; Blood measures

Introduction

To our knowledge the first descriptions of bisphosphonate-related osteonecrosis of the jaws (BRONJ) were published in 2003.¹ Since then it has become an increasingly recognised and problematic unwanted effect. It usually develops in patients who are being treated with nitrogen-containing bisphosphonates intravenously for metastatic bony deposits of malignant diseases such as breast, multiple myeloma, and prostate carcinoma, and the incidence is up to 18%.^{2,3}

BRONJ is often assumed to be primarily a condition of bone, although these drugs also directly affect mucous membranes. Bony metastases increase the activation of osteoclasts by production of various cytokines of tumour cells,⁴ which lead to clinical symptoms that include pain, pathological fractures, and hypercalcaemia. Bisphosphonates are potent inhibitors of osteoclast-mediated bony resorption⁵ and have been used for the past three decades to improve quality of life with considerable success.⁶ Although BRONJ is thought to be an avascular necrosis of the jaws, its precise aetiology remains unclear.

In most of our patients BRONJ developed after extraction of teeth. There are several mechanisms, such as anti-angiogenesis and toxic side effects of bisphosphonates, that inhibit wound healing.^{7,8} The role of bacterial infection is still not clear. Some authors think that *Actinomyces* has an

* Corresponding author at: Department of Oral and Maxillofacial Surgery, Klinikum Rechts der Isar der Technischen Universität München, Ismaninger Str. 22, 81675 München, Germany. Tel.: +49 89 4140 2921; fax: +49 89 4140 4993.

E-mail address: th.mucke@gmx.de (T. Mücke).

important role in the pathophysiology,^{9,10} whereas others do not.¹¹ A more probable effect might be deprivation of the innate immune system, including inhibition of the neutrophil enzymes that affect wound healing.^{8,11} The matrix metalloproteinase 8 of neutrophils that influences wound healing is inhibited by bisphosphonates¹² and an increased risk of neutropenia has been reported.¹³ In addition, the generation of formation of reactive oxygen species for the non-specific immune response is decreased by bisphosphonates,¹⁴ which affects the small guanosine triphosphatases (GTPases) that act as signalling proteins for the differentiation and function of neutrophils.¹⁵ There might be an adverse effect on the innate immune system with corresponding effects on the outcome after surgical treatment of BRONJ.

The purpose of this paper was to analyse the prognostic value of the white cell count and C-reactive protein concentration as potential predictors of recurrence after treatment.

Patients and methods

Subjects were recruited from the Department of Oral and Maxillofacial Surgery from 2007 to 2014. The same surgical team was responsible for all operations, and followed the same surgical protocol. The patients were evaluated prospectively, and investigated at least twice at six monthly intervals. The duration of exposure to bisphosphonates was measured in months from the initial dose until signs of BRONJ developed. We used the definition for BRONJ outlined by the American Association of Oral and Maxillofacial Surgeons. Criteria included current or previous treatment with bisphosphonates, exposed and necrotic bone in the maxillofacial region that had persisted for more than 8 weeks, and no history of radiotherapy to the jaws.⁷

Exclusion criteria were lack of adequate information, or the presence of confounding variables (for example, taking corticosteroids, history of radiotherapy, chemotherapy within the last 3 months, or metastases within the gingiva or jaws).

Diagnosis

BRONJ was diagnosed clinically according to the classification of Ruggiero et al.,¹⁶ and radiographically using dental panoramic tomograms and computed tomography. Complete clinical data were collected and classified. Intention to treat conservatively or surgically was based on the symptoms of each patient. Haematological variables were measured before surgical treatment was initiated.

Adjuvant conservative treatment

The antibiotics used depended on what had been given previously. An appropriate antibiotic was selected and given intravenously in each case. The regimen consisted of amoxicillin/sulbactam (3 g three times daily), or clindamycin

(600 mg three times daily) if the patient was allergic to penicillin.¹⁷ It was modified according to culture and sensitivity after appropriate sampling. The bisphosphonate was discontinued only if this was deemed to be in the best interests of the patient in relation to symptoms and progression of their original disease. Antiseptic mouth rinses with chlorhexidine were prescribed three times a day, and additional rinsing at least once daily, by the surgical staff.

Surgical treatment

Patients were operated on two weeks after the last dose of bisphosphonates (if they had not been discontinued), and the bisphosphonate was restarted no sooner than two weeks after operation. This did not seem to cause any disturbances in wound healing. The bone was routinely biopsied in all cases to confirm the diagnosis and to exclude metastatic disease.

The treatment of patients with BRONJ included sequestrectomy, debridement, and cleaning of the wound, depending on the stage and extent of the disease. After the incision of the periosteum the wound was closed without tension on the local (for example, mucoperiosteal) flap with interrupted resorbable sutures of 3/0 polyglactin 910 (Vicryl, Ethicon, Norderstedt, Germany).

Postoperative care

Postoperatively each patient was fed through a nasogastric tube for at least 5 days. The wounds were checked daily for signs of infection, breakdown, or recurrence of the disease. In cases of wound breakdown, the lesion was reassessed and treated either conservatively or surgically depending on the extent of healing. Sutures and the enteral feeding tube were removed routinely after 10 days.

Statistical analysis

Descriptive statistics for quantitative variables are given as mean (SD). If appropriate, medians and ranges were also computed. The data were analysed with the aid of SPSS for Windows (version 17.0, SPSS Inc, Chicago IL, USA).

Multiple logistic regression analysis was used to compute the factors that were independently associated with the dependent variable: recurrence of BRONJ. Covariates in this model were treatment-dependent variables of inflammation (C-reactive protein concentration, white cell count, or bacterial infection within the bone), extent of necrosis, location, type of treatment, and antibiotics used. 95% CI for estimated odds ratios (OR) that approximated the relative risk are also given. Tests were two-tailed, and probabilities of less than 0.05 were accepted as significant.

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